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Original article

Antiplasmodial and antitrypanosomal activities of aminobicyclo [2.2.2]octyl ω-aminoalkanoates

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Abstract

Several 4-aminobicyclo[2.2.2]octyl esters of ω-dialkylamino acids were prepared. Their activities against the multidrug-resistant K_1 strain of *Plasmodium falciparum* and *Trypanosoma brucei rhodesiense* (STIB 900) were determined using microplate assays and compared to those of formerly prepared analogues. The biological activity was influenced by the relative configuration in ring position 2, by the chain length of the acid moiety and by the amino substitution. The most active antiplasmodial ester was as active as chloroquine. One of the new compounds exhibited the highest antitrypanosomal activity and selectivity of all bicyclo-octane derivatives prepared so far.

Keywords: Bicyclo-octyl ester; 4-Aminobicyclo[2.2.2]octane derivative; In vitro assay; *Plasmodium falciparum*; *Trypanosoma brucei rhodesiense*

1. Introduction

Malaria and Human African Trypanosomiasis (HAT) are dangerous infectious diseases which are caused by eucaryotic parasites of the genera *Plasmodium* and *Trypanosoma*, respectively.

In 2004 malaria caused more than 1 million deaths [1]. From the four species of malarial parasites, the *Plasmodium falciparum* subspecies is the most virulent and potentially deadly organism. It is responsible for malaria tropica. Its multidrug-resistant strains are becoming prevalent around the world [1]. Possible in vitro and in vivo resistances have been demonstrated even against the most recently introduced artemisinin derivatives [2–4]. Therefore, new drugs with activity against drug-resistant strains are urgently needed.

In Sub-Saharan Africa about 40,000 people die annually because they fall ill with HAT [5]. More than 60 million people are at the risk of developing this disease, which is caused by the species of *Trypanosoma brucei* [6]. The more virulent *Trypanosoma brucei rhodesiense* causes East African sleeping sickness, whereas the West African form is elicited by *Trypanosoma brucei gambiense*. Without treatment every infection proceeds lethal. All four drugs in use (suramin, pentamidine, melarsoprol, eflornithine) cause severe side effects and have to be administered by partly painful injections. Melarsoprol, the only effective drug against the late stage of East African sleeping sickness, causes an encephalopathy in 10% of the patients, killing half of them [7]. Thus the development of new drugs against East African Trypanosomiasis is absolutely essential.

4-Aminobicyclo[2.2.2]octan-2-ols **2** have shown activity against a multiresistant strain of *P. falciparum* as well as against *T.b. rhodesiense* [8]. Compounds **2** were obtained in two steps from acyclic starting material via the corresponding ketones **1** [8,9]. Some of their ester derivatives **3** exhibit

Abbreviations: CC, column chromatography; CH_2Cl_2, dichloromethane; 4-DMAP, 4-dimethylaminopyridine; EtOH, ethanol; KI, potassium iodide; MeOH, methanol; NaOH, sodium hydroxide.

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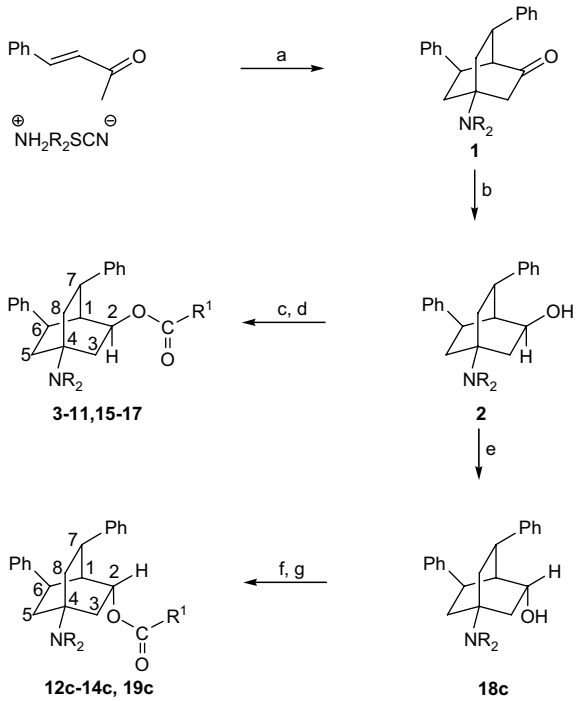
increased antiplasmodial and antitrypanosomal potencies [10–12]. So far the recently prepared bicyclo-octyl 2-aminoacetates **4**–**6** are the most potent in the ester series [13]. In order to investigate how the distance between the amino group and the bicyclic ring system influences the activities of these compounds, we inserted a methylene group into their carboxyl moiety synthesizing the corresponding 3-aminopropionates **7**–**9**. As a more hydrophilic alternative the ω-(4-hydroxypiperidino)alkanoates **10** and **11** were prepared. In addition selected epimers **12c**–**14c** of compounds **4**–**6** were synthesized. All new compounds were characterized and tested for their potencies against the K_1 strain of *P. falciparum* and *T.b. rhodesiense* using in vitro assays. Structure–activity relationships were derived from the comparison of the results with the activities of the corresponding 2-aminoacetates **4**–**6**.

2. Chemistry

The synthesis of bicyclo-octanones **1** from benzylidene acetone and dialkylammonium isothiocyanates succeeded via a one-pot procedure [8,9]. Their structures have been approved by a crystal structure analysis. Hydrogenation of compound **1** with lithium aluminium hydride gave stereoselectively the alcohols **2** which served as starting material for esterification. ω-Aminoalkanoates **4**–**11** were obtained from compound **2** via the corresponding ω-chloroalkanoates **15** and **16**. The latter were prepared by the treatment of compound **2** with the corresponding ω-chloroacyl chloride in the presence of 4-DMAP. Compounds **16** were always accompanied by a substantial quantity of secondary products, which were identified as acrylates **17** by means of NMR spectroscopy. However, a separation of chloropropionates **16** and acrylates **17** was not required. Both the compounds were smoothly converted to the 3-aminopropionates **7**–**9** by reaction with the corresponding secondary amine. The use of a solvent was sometimes required, whereupon the reaction period was considerably prolonged. In a likewise manner the 2-(4-hydroxypiperidino)alkanoates **10** and **11** were synthesized by the reaction of compounds **15** and **16** with 4-piperidinol using protic or polar-aprotic solvents (Scheme 1).

Bicyclo-octanol **18c** was prepared by the epimerization of compound **2c** in alkaline milieu in a two-step procedure [14]. The main part of alcohol **2c** was epimerized to **18c** upon heating with potassium *tert*-butoxide. The conversion was completed by the treatment of the isomeric mixture with sodium at ambient temperature. Acylation of compound **18c** with chloroacetyl chloride in the presence of 4-DMAP yielded compound **19c**, which was dissolved in excess amine to give the ω-aminoacetates **12c**–**14c**.

The configuration of compounds **7**–**11** was confirmed by through-space couplings from their 2-Hs to their 6-Hs in their NMR spectra. Likewise for compounds **12c**–**14c** NOEs were observed from aromatic *ortho*-protons to 2-H and 7-H. The bicyclic structure of compounds **7**–**14** was established by the typical w-couplings (2–3 Hz) between the protons in ring positions 3, 5 and 8 (Fig. 1).



Compounds	R^1
1, 2, 18c	----
3	*tert*-Bu, phenyl, naphthyl, benzyl, diphenylmethyl
4, 12c	diethylaminomethyl
5, 13c	pyrrolidinomethyl
6, 14c	piperidinomethyl
7	2-diethylaminoethyl
8	2-pyrrolidinoethyl
9	2-piperidinoethyl
10	4-hydroxypiperidinomethyl
11	2-(4-hydroxypiperidino)ethyl
15, 19c	chloromethyl
16	2-chloroethyl
17	vinyl

Scheme 1. Preparation of ω-aminoalkanoates **4**–**14**. Reagents and conditions: (a) toluene or DMF, 160 °C, 4 h; (b) $LiAlH_4$, ether, rt, 16 h; (c) ω-chloroalkanoyl chloride, 4-DMAP, CH_2Cl_2, rt, 2 days; (d) amine, KI, EtOH, rt, 30 min or amine, KI, CH_2Cl_2, rt, 16 h or amine, KI, rt, 30 min; (e) (1) potassium *tert*-butoxide, 200 °C, 24 h; (2) toluene, sodium, 100 °C to rt; (f) chloroacetyl chloride, 4-DMAP, CH_2Cl_2, rt, 16 h; (g) amine, KI, 4 °C, 2 days. **1a**–**11a**, **15a**–**17a**: NR_2 = dimethylamino; **1b**–**11b**, **15b**–**17b**: NR_2 = pyrrolidino; **1c**–**19c**: NR_2 = piperidino.

3. Antiplasmodial and antitrypanosomal activity

The new esters **7**–**14** were tested via microplate assays for their activities against the K_1 strain of *P. falciparum* (resistant to chloroquine and pyrimethamine) and *T.b. rhodesiense*. The cytotoxicity was determined with rat skeletal myoblasts (L-6 cells). Chloroquine, melarsoprol and podophyllotoxine were used as standards.

4. Results and discussion

Due to their 2-dialkylamino-substitution acetates **4**–**6** exhibit far better antiplasmodial and antitrypanosomal properties than their 2-unsubstituted analogues. Compounds **4b**, **4c** and **6c**